A SAFE, EFFECTIVE, HERBAL ANTISCHISTOSOMAL THERAPY DERIVED FROM MYRRH

ZAKI SHEIR, AMIRA A. NASR, AHMED MASSOUD, OSAMA SALAMA, GAMAL A. BADRA, HASSAN EL-SHENNAWY, NABIL HASSAN, AND SABY M. HAMMAD

Department of Internal Medicine, Faculty of Medicine, Department of Pharmacology, Faculty of Pharmacy, Students’ University Hospital, Urology and Nephrology Center, and Community Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt; Department of Tropical Medicine, Faculty of Medicine, Al Azhar University, Cairo, Egypt; Faculty of Medicine, Menoufeya Hepatology Institute, Shebene El-Kom, Menoufeya, Egypt

INTRODUCTION

Schistosomiasis is a widespread helminthic disease.1,2 Treatment of schistosomiasis is based on chemotherapy with praziquantel or oxamniquine.3-4 Praziquantel is the drug of choice because it is more effective than oxamniquine, especially for the treatment of mansoniasis.5 Drug resistance to praziquantel has been demonstrated by Brindley,6 Fallon and Doenhoff,7 Ismail and others,8 and Stelma and others.9 Based on these reports, an alternative safe and effective schistosomicidal drug is urgently needed. Herbal products are not only safe, but can also have effective antihelminthic activity. Ndamba and others10 found that extracts from Abrus precatorius (Leguminosae), Pterocarpus angolensis (Leguminosae), and Ocrooa insignis (Anacardiaceae) were lethal to adult Schistosoma hematobium. Myrrh is an oleo-gum resin from the stem of the plant Commiphora molmol. It is a safe, natural flavoring substance and has been approved by the U.S. Food and Drug Administration.11,12

In experimental studies on Swiss albino mice, myrrh from C. molmol showed no mutagenicity, and was found to be a potent cytotoxic drug against Ehrlich solid tumor cells with no clastogenic effect. The anti-tumor potential of C. molmol was comparable with that of the standard cytotoxic drug cyclophosphamide.13 Studies with hamsters demonstrated the anti-schistosomal activity of myrrh (Massoud A and others, unpublished data). Myrrh given to patients with active intestinal schistosomiasis complicated with hepatosplenomegaly was found to be safe and effective (Massoud A and others, unpublished data).

The aim of the present study was to assess the efficacy, toxicity, and side effects of myrrh, as well as to determine the most effective dosage schedule for the treatment of schistosomiasis in different stages of the disease.

PATIENTS, MATERIALS, AND METHODS

This study was carried out at the Urology and Nephrology Center at Mansoura University in Mansoura, Egypt between September 1998 and July 1999. It included 204 patients ranging in age from 12 to 68 years (mean ± SD = 37.9 ± 12.5 years). These included 169 males and 35 females selected randomly. Twenty healthy non-infected age- and sex-matched volunteers were also studied. All patients and volunteers gave informed consent prior to participating in the study. The protocol was reviewed and approved by the ethical committee of the Urology and Nephrology Center at Mansoura University.

Patient groups. The patients were divided into two groups. Group I was composed of 86 patients with schistosomal colitis ranging in age from 13.2 to 62 years (mean ± SD = 32.6 ± 12.9 years). Group II was composed of 118 patients with hepatosplenic schistosomiasis. The latter group was further divided into two subgroups. Subgroup IA was composed of 77 patients with compensated hepatosplenic schistosomiasis ranging in age from 12 to 58 years (mean ± SD = 40.2 ± 11.01 years) and subgroup IB was composed of 41 patients with decompensated hepatosplenic schistosomiasis ranging in age from 19 to 68 years (mean ± SD = 45.1 ± 9.5 years).

All patients had been previously treated with praziquantel except for 12 cases, four of whom were intolerant since they vomited immediately on ingesting the drug. Of the remaining patients, 156 received repeated courses of praziquantel at a dose of 50 mg/kg of body weight/day repeated three times (every other day). Thirty-six patients received one or two doses of praziquantel (40 mg/kg/day).

All patients provided a medical history and underwent a clinical examination with emphasis on symptoms before and after treatment. Routine liver and kidney function tests (i.e., serum bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and serum creatinine) were done, especially in cases of decompensated hepatosplenic schistosomiasis. A standard 12-lead electrocardiogram was done before and one week after starting treatment in 10 cases of decompensated hepatosplenic schistosomiasis who were given myrrh in a dose of 10 mg/kg/day for six days.

Diagnosis of schistosomiasis was based on the presence of living schistosoma ova either in urine, stool, or in colonic and rectal mucosal biopsies. Sigmoidoscopy and colonic and rectal mucosal biopsies.
rectal mucosal biopsies were done using a rigid sigmoidoscope (model no. 73332; Welch Allyn, New York, NY) before starting therapy to verify the presence of living schistosoma ova and to determine species (*S. hematobium*, *S. mansoni*, or mixed infections). Biopsies were repeated two months after the end of therapy to assess cure by demonstrating viability of the ova. Biopsy snips were examined by the transparency technique after being compressed between two glass slides.17

All patients and healthy volunteers were given a combination of resin and volatile oil extracted from myrrh at a dose of 10 mg/kg/day for three days on an empty stomach 1 hr before breakfast. Patients who still showed living ova two months after treatment in colonic plus rectal mucosal biopsy specimens were given a second course of 10 mg/kg/day for six days, and biopsy specimens were obtained two months later to assess cure. Twenty patients provided biopsy specimens six months after treatment.

### Statistical analysis

Statistical analysis of data was performed using the SPSS software package (SPSS, Inc., Chicago, IL). The Student’s paired *t*-test and the Wilcoxon signed rank test were used to compare parametric and non-parametric quantitative variables before and after therapy. Multivariate regression analysis, the chi-square test, or Fisher’s exact tests were used. All reported *P* values were two-tailed. Statistical significance was set at a *P* value < 0.05.

### RESULTS

The response to a single course of myrrh (10 mg/kg/day for 3 days) in relation to demographic, clinical, and biochemical colonic and rectal mucosal biopsy data is shown in Tables 1, 2, and 3. Based on these findings, none of these factors was a predictor for a response to myrrh.

The cure rate was 91.7% in 187 patients (155 males and 32 females), of whom 51 were less than 30 years of age and...
136 were more than 30 years old. The cure rate was 90.7%, 93.5%, and 90.2% in patients with schistosomal colitis, compensated and decompensated hepatosplenic schistosomiasis, respectively.

All 12 patients who had never been treated with praziquantel were cured with a single course of myrrh (10 mg/kg/day for 3 days [cure rate = 100%]), whereas the cure rate was less in patients who had been previously treated with praziquantel: 91.7% and 88.9%, respectively, for those who received complete and incomplete courses of praziquantel (Table 1). The cure rate was always less in patients with impaired liver function compared with those with normal liver function test results, but the differences were not statistically significant. (P > 0.05; Table 3).

All four cases with only a S. hematobium infection were cured. The cure rate in mixed S. hematobium and S. mansoni infections was 93.1% compared with 91.2% in those infected only with S. mansoni (Table 2).

Of 204 patients studied, 185 (90.7%) showed complete improvement of symptoms, 13 (6.4%) showed partial improvement, and six (2.9%) reported no improvement (Table 4). In patients with normal liver functions (ALT, AST, and serum bilirubin), no significant changes were observed in these functions after treatment with myrrh (P > 0.05). On the other hand, patients with impaired liver function showed significant improvements in the elevated levels of serum ALT and AST (P < 0.05; Table 5) but no significant decrease in serum bilirubin (P > 0.05; Table 5). Although serum creatinine levels remained within the normal range, they showed a significant decrease after therapy with myrrh (P < 0.05; Table 5).

There was no significant effect of treatment with myrrh on the electrocardiographic parameters in 10 cases one week after starting therapy (P > 0.05; Table 6).

Multivariate regression analysis showed that no factor was a predictor of the response to myrrh with regard to age, sex, body weight, history of treatment with praziquantel, presence of decompensated liver disease, or type of schistosomiasis infection.

Side effects of myrrh are shown in Table 7. Of 204 cases, no side effects were reported in 180 cases (88.2%). Giddiness, somnolence, or mild fatigue were the most frequently encountered side effects (2.5%), whereas all other side effects were minor and less frequent. None of the healthy volunteers reported any side effects, nor was there any significant change in liver or kidney functions (Table 8).

After a single course of myrrh treatment 10 mg/kg/day for three days, the cure rate was 91.7%, whereas in the remaining 17 non-responding cases, a second course of myrrh (10 mg/kg/day for 3 days) resulted in a cure rate of 76.5%. The overall cure rate was 98.09% (Table 9).

**DISCUSSION**

Schistosomiasis, a grave and debilitating disease of socioeconomic importance, is increasing despite concerted efforts.

### Table 4
Symptomatic improvement after a single course of myrrh (10 mg/kg of body weight/day for 3 days) in studied patients (n = 204)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved completely</td>
<td>185 (90.7)</td>
</tr>
<tr>
<td>Improved partially</td>
<td>13 (6.4)</td>
</tr>
<tr>
<td>No improvement</td>
<td>6 (2.9)</td>
</tr>
</tbody>
</table>

### Table 5
Effect of treatment with myrrh on liver and renal functions*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No.</th>
<th>Before</th>
<th>After</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired liver function</td>
<td></td>
<td>Median (range)</td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>28</td>
<td>1.45 (1–6.9)</td>
<td>1.4 (1–4.5)</td>
<td>0.206NS</td>
</tr>
<tr>
<td>ALT (U/ml)</td>
<td>30</td>
<td>91 (45–211)</td>
<td>63 (17–204)</td>
<td>0.001*†</td>
</tr>
<tr>
<td>AST (U/ml)</td>
<td>32</td>
<td>90.5 (45–240)</td>
<td>70 (23–218)</td>
<td>0.013§</td>
</tr>
<tr>
<td>Normal liver function</td>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>54</td>
<td>0.83 ± 0.14</td>
<td>0.82 ± 0.18</td>
<td>0.569NS</td>
</tr>
<tr>
<td>ALT (U/ml)</td>
<td>52</td>
<td>28.5 ± 8.2</td>
<td>27.4 ± 7.3</td>
<td>0.249NS</td>
</tr>
<tr>
<td>AST (U/ml)</td>
<td>50</td>
<td>27.5 ± 8.6</td>
<td>26.7 ± 7.9</td>
<td>0.34NS</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td>Serum creatinine (mg/dl)</td>
<td>34</td>
<td>0.97 ± 0.17</td>
</tr>
</tbody>
</table>

* ALT = alanine aminotransferase; AST = aspartate aminotransferase; NS = not significant.
† Calculated using the Wilcoxon signed rank test.
‡ P < 0.01.
§ P < 0.05.
$ Calculated using the paired t-test.

### Table 6
Effect of treatment with myrrh on electrocardiographic parameters among studied patients (n = 10)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before X ± SD</th>
<th>After X ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (beats/min.)</td>
<td>70.9 ± 8.91</td>
<td>75.2 ± 12.36</td>
<td>0.184</td>
</tr>
<tr>
<td>Axis (0)</td>
<td>34.0 ± 32.64</td>
<td>32.2 ± 27.2</td>
<td>0.713</td>
</tr>
<tr>
<td>P-R interval (sec)</td>
<td>0.18 ± 0.03</td>
<td>0.178 ± 0.029</td>
<td>0.780</td>
</tr>
<tr>
<td>P wave duration (sec)</td>
<td>0.118 ± 0.006</td>
<td>0.109 ± 0.014</td>
<td>0.095</td>
</tr>
<tr>
<td>P wave amp (mv)</td>
<td>0.165 ± 0.053</td>
<td>0.160 ± 0.046</td>
<td>0.678</td>
</tr>
<tr>
<td>QRS duration (sec)</td>
<td>0.074 ± 0.016</td>
<td>0.069 ± 0.014</td>
<td>0.1</td>
</tr>
<tr>
<td>QRS amp (mv)</td>
<td>0.825 ± 0.190</td>
<td>0.890 ± 0.264</td>
<td>0.266</td>
</tr>
<tr>
<td>ST seg. (sec.)</td>
<td>0.154 ± 0.027</td>
<td>0.145 ± 0.042</td>
<td>0.510</td>
</tr>
<tr>
<td>T wave duration (sec)</td>
<td>0.137 ± 0.029</td>
<td>0.130 ± 0.017</td>
<td>0.539</td>
</tr>
<tr>
<td>T wave amp (mv)</td>
<td>0.275 ± 0.063</td>
<td>0.295 ± 0.064</td>
<td>0.319</td>
</tr>
<tr>
<td>QT-c (sec)</td>
<td>0.446 ± 0.011</td>
<td>0.431 ± 0.027</td>
<td>0.101</td>
</tr>
</tbody>
</table>
to control and contain the disease in all endemic areas. Schistosomicides such as antimonials were introduced as early as the 1900s and used until the 1960s. Because of severe side effects, antimonials were replaced by hycanthone and luchanotide, but these drugs produced immediate side effects such as hepatotoxicity and gastrointestinal disturbances, and were withdrawn. Niridazole, oxamniquine, and metrifonate were introduced, including Oltipraz and Amoscanate. However, therapeutic doses of these drugs were found to cause major side effects. A significant advance in the control of schistosomiasis chemotherapy was the introduction of praziquantel, but resistance to this drug is an emerging problem.7,9–12 Mass treatment, a crucial goal in the eventual control of schistosomiasis, awaits a well-tolerated and non-toxic drug.

In the current study, myrrh was given to 300 patients and 20 healthy volunteers; 204 patients completed the study. We found that the disease was more common in males (82.8%), which was probably due to a higher chance of exposure to infection. Schistosomiasis was resistant to praziquantel in 156 patients who received repeated intensive courses of praziquantel (50 mg/kg/day, 3 times at day, every other day). These patients were living under the same conditions when given myrrh in the current study. Complete clinical improvement was observed in 90.7% of the patients. We noted that the 20 patients who provided biopsy specimens six months after treatment with myrrh still showed no living schistosome ova.

Multivariate regression analysis showed that no factor was a predictor of the response to myrrh with regard to age, sex, body weight, history of treatment with praziquantel, presence of decompensated liver disease, or type of schistosomiasis infection.

The cure rate was lower in patients who had previously received praziquantel (88.9% for incomplete and 91.7% for complete courses of praziquantel versus 100% for those who had never received praziquantel). This may be due to tolerance of the schistosomes to myrrh induced by previous treatment with praziquantel.

Although patients with impaired liver function improved significantly with regard to the levels of liver enzymes, they still had lower cure rates than individuals with normal liver functions (82.1–84.4% versus 92.0–92.6%). Although the difference did not reach statistically significance, we speculate that it may be due to better absorption and metabolism of the drug in patients with normal liver function compared to those with impaired liver function. Myrrh contains many volatile oils that are fat-soluble and requires bile salts for absorption. Whether myrrh is metabolized to more active ingredients by the liver still awaits further investigations. This notion is supported by the relatively lower cure rates in jaundiced patients (87.5%) compared with patients with compensated hepatosplenic schistosomiasis (93.5%) or schistosomal colitis alone (90.7%).

Patients in the younger age group had a higher cure rate than the older age group (94.4% versus 90.7%). Although this difference did not reach statistical significance, it may be due to less frequent exposure of the younger age to multiple courses of antischistosomal treatments and a lesser chance for development of resistant parasites. The healthier liver functions of this young age group may also facilitate absorption and metabolism of the drug.

Infection with S. hematobium infection was the most responsive to treatment, followed by mixed infections. Those infected with S. mansoni had the lowest cure rate (91.2%). This may be overshadowed by the higher percentage of S. mansoni infections in the studied patients (171 of 204, 83.8%), and may not reflect the actual response of S. mansoni to myrrh. Despite this, we speculate that S. hematobium is more susceptible to myrrh than S. mansoni.

Side effects of myrrh were transient and mild and occurred in only 11.8% of the treated cases and in none of the healthy volunteers. The most frequently reported side effects were giddiness, somnolence, mild fatigue, and abdominal pain or discomfort. The four patients that were intolerant to praziquantel tolerated myrrh with no side effects. Myrrh had not significant. The P value was not significant.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>204 (100.0)</td>
</tr>
<tr>
<td>None</td>
<td>180 (88.2)</td>
</tr>
<tr>
<td>Epigastric pain/heartburn</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Diarrhea/loose stool</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Polyurea</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Fleeting aches</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Giddiness/somnolence</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Generalized itching</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

### Table 7

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>204 (100.0)</td>
</tr>
<tr>
<td>None</td>
<td>180 (88.2)</td>
</tr>
<tr>
<td>Epigastric pain/heartburn</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Diarrhea/loose stool</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Polyurea</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Fleeting aches</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Giddiness/somnolence</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Generalized itching</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

### Table 8

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Mean ± SD</th>
<th>After Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (U/ml)</td>
<td>20.8 ± 4.5</td>
<td>22.3 ± 5.8</td>
</tr>
<tr>
<td>AST (U/ml)</td>
<td>27.2 ± 6.4</td>
<td>31.2 ± 6.4</td>
</tr>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.3</td>
</tr>
</tbody>
</table>

### Table 9

<table>
<thead>
<tr>
<th>Response of studied patients to treatment with myrrh</th>
<th>Total No.</th>
<th>Cured No. (%)</th>
<th>Not cured No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After single course (3 days)</td>
<td>204</td>
<td>187 (91.7)</td>
<td>17 (8.3)</td>
</tr>
<tr>
<td>After second course (6 days)</td>
<td>17</td>
<td>13 (76.5)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Overall response</td>
<td>204</td>
<td>200 (98.1)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>
Authors’ addresses: Zaki Sheir, Urology and Nephrology Center, Mansoura University, El-Gomhoria Street, Mansoura 35516, Egypt. Amira A Nasr, Department of Internal Medicine, Mansoura Faculty of Medicine, El-Gomhoria Street, Mansoura, Egypt. Ahmed Masoud, Department of Tropical Medicine, Al-Azhar Faculty of Medicine, District 6, El-Mokhayam El-Daem Street, Nasr City 11184, Cairo, Egypt. Osama Salama, Department of Pharmacology, Mansoura Faculty of Pharmacy, El-Gomhoria Street, Mansoura, Egypt. Gamal A. Badra, Hepatology Department, Liver Institute, Menofeya University, Yassin Abdelghafar Street, Shebin El-Kom, Menofeya, Egypt. Hassan El-Shenawy, Department of Internal Medicine, Students’ University Hospital, Mansoura University, El-Gomhoria Street, Mansoura, Egypt. Nabil Hassan, Department of Nephrology, Urology and Nephrology Center, Mansoura University, El-Gomhoria Street, Mansoura 35516, Egypt. Sabry H. Hammad, Community Medicine Department, Mansoura Faculty of Medicine, El-Gomhoria Street, Mansoura, Egypt. Reprint requests: Zaki Sheir, Urology and Nephrology Center, El Gomhoria Street, Mansoura 35516, Egypt.

REFERENCES


